

Frequent Dose of Peginterferon Alfa 2a Evaluation in Treatment-Naïve Chronic HCV, Genotype 4 Egyptian Patients

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Abstract

Introduction: More frequent dosing with decreasing time intervals between injections of pegylated interferon in the treatment of HCV genotype 4, to our knowledge, was not tested before. The purpose of reducing the intervals between doses particularly in the first 12 weeks is to decrease the peak/trough ratio of the blood concentration of interferon in order to give no chance for the virus to recover. Therefore, **the aim** of this study is to explore the effect of such frequent dosing in the first 12 weeks as a trial to increase the response rates of our Egyptian patients with HCV genotype 4.

Materials and methods: This study includes 28 Egyptian patients, discovered to have chronic hepatitis C genotype 4 infection within 1-11 years before enrolling to study. They include 17 males and 11 females with mean age 41.57. Patients with active HCV infection without any vascular or parenchymatous decompensation were given pegasys 180µg every 5 days and ribavirin according the weight (800-1400 mg/day) for the first 4 injections. PCR is then done. Those with RVR (negative PCR after 4th injection) were treated in usual way with pegasys given every week. Those with detectable HCV RNA continued in the same way as first month for 12 injections. PCR was then repeated. Those showing EVR continued treatment in the usual way. Those with partial or slow EVR (detected HCV but viral load decreased at least 2 logs) continued as first month for 24 injections. Those with non EVR stopped treatment. All other patients continued treatment till 48 injections. Re-evaluation was done at end of treatment and after 6 and 12 months of end of treatment.

Results: Rapid virological response with disappearance of HCV RNA after 4 injections of treatment was detected in 14 cases (50%) in whom treatment in usual way continued till the end of 48 weeks. Additional 8 patients (28.6%) showed disappearance of HCV after 12 weeks of treatment to reach total of 22 cases (78.6%) in whom treatment in usual way continued till the end of 48 weeks. Three patients showed 2 log reduction of viral load continue treatment per protocol while 3 patients showed less viral load reduction were withdrawn from treatment. Additional 2 patients showed disappearance of HCV RNA at 24 weeks of treatment to reach a total of 24 patients (85.7%) the patient showing positive RNA stopped treatment. All those patients continuing treatment to 48 weeks remain negative for HCV RNA at end of treatment. Therefore, the ETR is 85.7% using this frequent dose administration of pegylated interferon. Only one patient relapse at week 72 (after 6 months of end of treatment). Thus, the SVR occurred in 23/28 patient (82.14%). Dose reduction was done for Ribavirin in 3 cases during treatment due to clinically significant decrease in the hemoglobin levels, all showed SVR. No reduction of interferon dose was commenced. General side effects were as usual and controlled with paracetamol.

Conclusion: It is concluded that the use of more frequent peginterferon is associated with the best SVR in genotype 4, and whenever possible this strategy can be used particularly in patients with early disease as indicated by absence of sever hepatic or hematological abnormalities.

Keywords: Chronic HCV, Genotype 4, Peginterferon Alfa 2a.

Introduction

HCV is endemic in most regions of the world and has an estimated global prevalence as high as 3%, affecting up to 170 million people worldwide⁽¹⁾. Although certain regions, such as northern Africa and the eastern Mediterranean, including Egypt, have a very high prevalence of HCV infection relative to other areas, it is currently the most common chronic blood-borne

infection in the USA with a prevalence of approximately 1.3%, leading to chronic liver disease in an estimated 3.2 million individuals⁽⁴⁾. Also, chronic HCV infection is a major source of liver-related morbidity and mortality, resulting in progressive liver disease, cirrhosis and HCC in many individuals and HCV-associated liver failure is the leading indication for liver transplantation, accounting

for 40-50% of all liver transplants in the USA^(2,3). Chronic HCV is a major public health problem in Egypt and, more than 90% of patients were genotype 4⁽²³⁾. Early treatment of chronic HCV patients will markedly reduce progression to cirrhosis, decompensated disease and hepatocellular carcinoma⁽²⁴⁾.

Combination therapy with either peg-IFN- α -2a or peg-IFN- α -2b and ribavirin (RBV) currently remains the gold standard in the treatment of chronic HCV infection^(5,6). Despite advances in IFN-based therapy over the last 14 years, the ability to achieve a sustained virologic response (SVR), defined by the suppression of HCV RNA to undetectable levels on treatment and 6 months following completion of therapy, is limited to approximately 50% of patients in all genotypes^(7,8). The initial landmark clinical trial of combination peg-IFN and RBV for chronic hepatitis C reported an SVR in up to 52% of patients with genotype 1 infection following a 48-week course of therapy, while genotype 2 and 3 patients achieved an SVR in as many as 84% of patients with a shorter duration of therapy of 24 weeks^(9,10,11). The use of weight-based RBV in the treatment of genotype 1 infection is well-established and is superior to flat-dose administration, as demonstrated in a large prospective clinical trial⁽¹²⁾. By contrast, a higher RBV dose or weight-based dosing does not have a significant impact on efficacy in genotype 2 or 3 infection⁽¹³⁾.

In patients with detectable HCV RNA at week 12, who proceed to clear HCV RNA by week 24, known as 'slow responders', prolonging the period of complete viral suppression by extending the course of therapy to 72 weeks may have a favourable impact on the rate of SVR and should be considered in these individuals⁽¹⁴⁻¹⁶⁾, although, one recent prospective study did not demonstrate a significant advantage with an extended treatment duration⁽¹⁷⁾. Many studies suggest that individualization of peginterferon/ribavirin treatment for chronic hepatitis C based on responses during the first 12 weeks of therapy can improve virologic outcomes⁽¹⁸⁻²⁰⁾. For example, patients with genotype 1/4 HCV and a rapid virologic response (i.e., undetectable HCV RNA after 4 weeks of treatment) may be able to reduce the standard duration of peginterferon/ribavirin treatment from 48 to 24 weeks without compromising sustained virologic response (SVR) rate^(1,2), thereby reducing costs and

treatment-related adverse events. By contrast, patients who exhibit a slow virologic response after 12 weeks of treatment may benefit from extended-duration therapy to improve the chance for SVR⁽²⁰⁻²²⁾.

More frequent dosing with decreasing time intervals between injections of pegylated interferon, to our knowledge, was not tested before. The purpose of reducing the intervals between doses particularly in the first 12 weeks is to decrease the peak/trough ratio of the blood concentration of interferon in order to give no chance for the virus to recover. Therefore, the aim of this study is to explore the effect of such frequent dosing in the first 12 weeks as a trial to increase the response rates of our Egyptian patients with HCV genotype 4.

Materials and methods:

This study includes 28 Egyptian patients, discovered to have chronic hepatitis C genotype 4 infection within 1-11 years before enrolling to study. They include 17 males and 11 females with mean age of 41.57 years.

Exclusion Criteria: clinical or biochemical evidence of hepatic decompensation or portal hypertension, history of severe psychotic disorder, disturbed thyroid function, Hb <12mg/dl, platelets <100,000/mm³, WBCs < 1500/cmm, the presence of autoimmune disease, history of organ transplantation, viral therapy or immunosuppressive drugs, history of previous antiviral treatment of HCV, any major medical illness including cardiac, pulmonary, renal, or neurological diseases and non-willing to complete the study.

All Patients were subjected to the following

- 1- Thorough medical evaluation including history taking, general and abdominal examination with special stress for manifestations of chronic liver disease or other medical illness.
- 2- Biochemical assessment including complete blood picture, complete liver profile, prothrombin time, alfa-fetoprotein, renal function, fasting blood sugar,
- 3- If indicated, thyroid hormones, autoimmune markers, HBsAg, HDV Ab, or others.
- 4- Those with positive HCV Ab are subjected to quantitative HCV RNA by RT-PCR (Amplicor Molecular System, F Hoffmann - La Roche, Basel -Switzerland) and genotyping by the Inno Lippa HCV II assay (innogenetics inc., GA, USA).

- 5- Liver biopsy if indicated providing pathological criteria of chronic HCV hepatitis or cirrhosis.

Serum alanine aminotransferase (ALT) was done by autoanalyzer dimension expressed as U/L. ANA and AMA were done by the indirect immunofluorescence antibody test for detection and quantitation of ANA and AMA (The Binding site LTD, Birmingham, England)

Study design:

Patients with active HCV infection without any vascular or parenchymatous decompensation were given pegasys 180µg every 5 days and ribavirin according to the weight (800-1400 mg/day) for the first 4 injections. PCR is then done. Those with RVR (negative PCR after 4th injection) were treated in usual way with pegasys given every week. Those with detectable HCV RNA continued treatment in the same way as with injection every 5 days for 12 injections. PCR was then repeated. Those showing EVR

continued treatment in the usual way. Those with partial or slow EVR (detected HCV but viral load decreased at least 2 logs) continued with injection every 5 days for 24 injections. Those with non EVR stopped treatment. All other patients continued treatment till 48 injections. Re-evaluation was done at end of treatment and after 6 and 12 months of end of treatment. Follow up during treatment was done in usual way with repeated liver function tests, complete blood picture, PT, and other tests according to the case. The dose of ribavirin was modulated according to the haemoglobin level during treatment and dose of pegylated interferon according to platelet and white blood cell counts. **Statistical analysis:** continuous variables, expressed as mean \pm SD, were compared by using student's t-test or correlated by using simple regression done by Excel program. Differences were considered significant if $P < 0.01$.

Results:

This study included 28 Egyptian patients; the sex and age are plotted in tables 1 and 2.

Table 1: Sex distribution of study group

	Frequency	Percent
Males	17	60.7
Females	11	39.3
Total	28	100.0

Table 2: Mean age of study group

Mean	Std. Deviation
41.57 yrs	9.10608

Table 3: Laboratory findings before treatment

	ALT U/L before treatment	AST U/L before treatment	PCR IU/ml before treatment	HB gm/dl before treatment	WBC thousand/cubic mm before treatment	Platelets thousand/cubic mm before treatment	Bilirubin mg/dl before treatment
Mean	96.32	83.64	3304642.86	14.75	5684.29	207.43	1.28
SD	40.88	33.641	3288817.64	1.133	1841.26	58.57	.638

Table 4: Laboratory findings 4 weeks after treatment

	ALT	AST	PCR	HB	WBC	Platelets	Bilirubin
Mean	42.68	43.68	226994.64	13.31	4440.64	162.71	1.40
SD	23.28	19.26	864125.014	1.266	1297.22	49.98	0.65

Rapid virological response with disappearance of HCV RNA after 4 weeks of treatment was

detected in 14 cases (50%) in whom treatment in usual way continued till the end of 48 weeks.

Table 5: Laboratory findings 12 weeks after treatment

	ALT	AST	PCR	HB	WBC	Platelets	Bilirubin
Mean	36.64	48.29	348878.93	13.51	5319.11	157.68	1.46
SD	22.16	26.01	1419790.77	0.917	7853.98	46.65	0.426

Additional 8 patients (28.6%) showed disappearance of HCV after 12 weeks of treatment to reach total of 22 cases (78.6%) in whom treatment in usual way continued till the end of 48 weeks. Three patients showed 2 log reduction of viral load continue treatment per protocol while 3 patients showed less viral load reduction were withdrawn from treatment.

Table 6: Laboratory findings 24 weeks after treatment

	ALT24	AST24	PCR24	HB24	WBC24	Platelets24	Bilirubin24
Mean	34.61	42.82	298144.64	13.22	3785.00	166.39	1.30
SD	24.15	24.17	960402.95	0.78	678.95	38.56	0.25

Additional 2 patients showed disappearance of HCV RNA at 24 weeks of treatment to reach a total of 24 patients (85.7%), the patient showing positive RNA stopped treatment.

Table 7: Laboratory findings 48 weeks after treatment

	ALT	AST	PCR	Hemoglobin	WBC	Platelets	Bilirubin
Mean	28.88	41.84	0.00	13.23	4164.32	160.76	1.37
SD	5.69	6.53	0.00	0.97	1229.71	52.89	0.54

All those patients continuing treatment to 48 weeks remain negative for HCV RNA at end of treatment. Therefore, the ETR is 85.7% using this frequent dose administration of pegylated interferon.

Table 8: Laboratory findings 72 weeks after treatment

	ALT	AST	PCR	HB	WBC	Platelets	Bilirubin
Mean	30.04	39.12	10780.00	13.18	3998.72	151.40	1.12
SD	10.38	9.92	53900.00	0.86	746.89	41.138	0.29

Only one patient relapse at week 72 (after 6 months of end of treatment). Thus, the SVR occurred in 23/28 patient (82.14%)

The biochemical and hematological response to treatment are shown in the last 6 tables. Dose reduction was done for Ribavirin in 3 cases during treatment due to clinically significant decrease in the hemoglobin levels, all showed SVR. No reduction of interferon dose was commenced. General side effects were as usual and controlled with paracetamol.

Discussion:

Among the pretreatment factors that may influence the response to therapy in HCV, the HCV

genotype and (to a lesser extent) HCV RNA level will most accurately predict whether the patient will attain a SVR. Multiple studies have shown that patients with genotype 2 or 3 HCV clearly have better SVR rates than those with genotype 1 HCV. Additional data have shown that patients also have more favorable SVR response rates if they have "low" baseline HCV RNA levels (less than 2×10^6 copies/ml or 800,000 IU/ml) ^(25,26,27).

The specific regimen used and the duration of therapy will also affect SVR rates. With respect to treatment duration, available data suggest that patients with genotype 1 HCV have better SVR rates with 48 weeks of therapy than with 24 weeks, whereas patients with genotypes 2 and 3 have a similar SVR rates with 24 or 48 weeks of therapy ^(25,28).

In 2009, investigators identified a genetic polymorphism at the IL28B gene encoding interferon-lambda-3 and reported its association with spontaneous clearance of the virus during acute infection as well as with treatment responses to interferon-based HCV therapy for genotype 1 infection. The distribution of IL28B alleles explains part of the variability in treatment responses observed among different racial groups. The CC genetic variant in particular is correlated with favourable treatment response and a 5.2-fold greater likelihood of SVR than with other variants ^(29,30).

In this study, decreasing time intervals between injections of pegylated interferon was conducted in the first 4-24 weeks, according the viral response, to decrease the peak/trough ratio of the blood concentration of interferon. This might not allow the virus to recover. The study included 28 Egyptian patient with HCV genotype 4 in whom the average sustained response rate is around 50% using the standard regimens of pegylated IFN and ribavirin ⁽³¹⁻³⁶⁾. Patients of this study were chosen thoroughly without showing any signs of parenchymatous or vascular hepatic or haematological derangements to allow using of more frequent interferon doses. All patients were treated according the protocol with no major adverse events to be withdrawn from treatment. Few patients showed reduction of haemoglobin in whom the dose was reduced and all showed sustained virological response.

The SVR occurred in 23/28 patient (82.14%) which is the highest response rate seen

in HCV genotype 4 in all studies mentioned before. The study populations were homogenous and did not show any signs of severe liver disease and were able to continue treatment throughout the study.

It is concluded that the use of more frequent peginterferon is associated with the best SVR in genotype 4, and whenever possible this strategy can be used particularly in patients with early disease as indicated by absence of sever hepatic or hematological abnormalities.

It is recommended from this study to increase the frequency of interferon doses in those with no hepatic or hematological derangements in order to increase the SVR rate and to avoid the retreatment with additional oral antivirals which have the potentials of more costs, more side effects and development of viral resistance. Also, future studies in those with more advanced liver disease might be tried, even with 6- day's intervals.

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